Clinical Expert Series CME

Sepsis and Septic Shock During Pregnancy and Postpartum

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Sepsis and septic shock are leading causes of maternal morbidity and mortality. Sepsis complicates an estimated 1 in 1,000 pregnancies and is responsible for 24% of in-hospital maternal deaths. Because most cases occur outside of the hospital, it is crucial to educate patients about warning signs to seek early medical care and for clinicians to engage in critical listening and evaluation of patient concerns. In the hospital, screening patients for vital sign aberrancy, followed by bedside and laboratory evaluation for signs of end-organ injury, prompt antibiotic therapy, and restoration of perfusion (through fluid resuscitation and vasopressor administration), is critical for optimal outcomes. Long-term sequelae are common and include psychological sequelae, cognitive dysfunction, and weakness. Screening for these long-term effects and referrals for treatment are key to patient recovery.

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According to the most recent report from the Centers for Disease Control and Prevention,[1] sepsis is the leading cause of pregnancy-related mortality. It is important to note that most of these deaths are believed to be preventable through early identification and treatment.[2] Physiologic changes of pregnancy overlap with early sepsis-induced vital sign abnormalities, making it more difficult for pregnant patients with sepsis to stand out until later in the disease process. The purpose of this article is to review the epidemiology, common causes, clinical pearls for screening, diagnosis, treatment, and long-term sequelae of sepsis during pregnancy and postpartum.

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DEFINITION AND PATHOPHYSIOLOGY

Sepsis is defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[3] *Septic shock* is defined as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone."[3] Furthermore, the diagnosis of septic shock requires the use of vasopressors and an elevated serum lactate above 2 mmol/L after adequate fluid resuscitation. Hemodynamically, cytokine-induced nitric oxide production by the endothelium results in profound vasodilation (decreased systemic vascular resistance) and systemic hypotension (distributive shock).[4] Hypotension is worsened by diffuse endothelial and glycocalyx injury (mediated by cytokines, elastases, proteases), resulting in third spacing with relative hypovolemia.[5] Although cardiac output is frequently increased as a result of minimal afterload, the heart is profoundly affected during sepsis (septic cardiomyopathy) with development of either systolic or diastolic dysfunction.[6] Systolic dysfunction is induced by direct myocardial contractile inhibition from cytokines; diastolic dysfunction may occur as fluid third spaces within the free wall of the left ventricle, obliterating its cavity and limiting diastolic preload filling.[6,7]

Simultaneously, activated inflammatory cells (eg, monocytes, neutrophils, macrophages) express tissue

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factor on their surfaces binding factor VII with activation of the clotting cascade through the extrinsic pathway.[8] The latter leads to diffuse formation of microthrombi with end-organ ischemia (thrombotic disseminated intravascular coagulation).[8] Finally, the lack of organ perfusion is aggravated by cytokine-induced mitochondrial dysfunction with accumulation of lactate as a result of anaerobic metabolism.[9] Mitochondrial dysfunction can cause cytopathic hypoxia or inability to use the oxygen available.[10] The pathophysiology of sepsis is summarized in Figure 1.

Clinically, these pathophysiologic changes result in organ hypoperfusion leading to multiple organ failure (eg, confusion, pulmonary edema, systemic hypotension, liver and kidney injury, ileus, bone marrow dysfunction). Because early sepsis may not manifest all traditional signs and symptoms, clinicians must maintain a high index of suspicion. For example, decreased perfusion can present as difficulty in obtaining pulse oximetry measurements as a result of a poor-quality waveform. Similarly, hypothermia, which is associated with worse outcomes, may be identified by an inability to accurately measure temperature. Increased oxygen requirements without explanation may be the result of mitochondrial dysfunction. Tachypnea, even in the absence of hypoxemia, frequently is a compensatory response to lactic acidosis. Unfortunately, respiratory rate is often not measured or documented accurately.[11,12] Fever or hypothermia may not be present in 20–25% of pregnant or postpartum patients with sepsis, even in the most severe cases resulting in death.[2,13,14] In patients with preeclampsia, hypotension may be less apparent because of elevated baseline blood pressure. In addition, tachycardia may not be present in patients taking labetalol as a result of β1 blockade. Given challenges with the recognition of sepsis, clinical alert systems may want to alert for missing vital sign measurements, which could indicate difficulties in obtaining measurements. Nurses should also alert clinicians when vital signs are difficult to obtain, helping to ensure timely recognition and intervention for sepsis.

EPIDEMIOLOGY

There are challenges with identifying the incidence of sepsis throughout pregnancy and postpartum. Most population-based articles reporting the incidence of sepsis cases focus on one cross-section in time such as the delivery hospitalization or postpartum readmissions rather than the entirety of pregnancy and the postpartum period. In addition, many studies do not include more recent data after the release of the Sepsis-3 (Third International Consensus Definitions for Sepsis and Septic Shock) definition in 2016. Most recent estimates (2016 and later) indicate that the incidence during antepartum is 1:855, during the delivery hospitalization is between 1:478 and 1:2,500, and during the postpartum period is 1:769 to 1:840.[15–17] Temporal trends indicate that sepsis is increasing during delivery hospitalization but not during the postpartum period.[16] In state-wide California data, most cases occurred outside of the hospital; 23.6 sepsis cases per 10,000 deliveries presented during antepartum and postpartum readmissions compared with 20.6 sepsis cases per 10,000 deliveries during the delivery hospitalization.[15] A study using the national readmissions database found an incidence of 1.1 sepsis cases per 1,000 deliveries during the delivery hospitalization compared with 1.3 sepsis cases per 1,000 deliveries presenting during the postpartum readmission.[16] Sepsis is a significant cause of in-hospital maternal mortality and was associated with

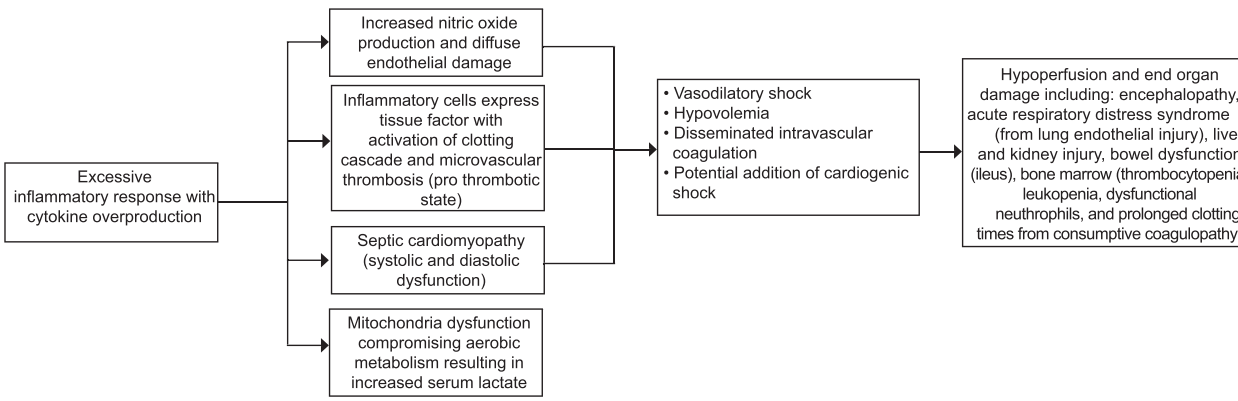
Excessive inflammatory response with cytokine overproduction
Increased nitric oxide production and diffuse endothelial damage
Inflammatory cells express tissue factor with activation of clotting cascade and microvascular thrombosis (pro thrombotic state)
Septic cardiomyopathy (systolic and diastolic dysfunction)
Mitochondria dysfunction compromising aerobic metabolism resulting in increased serum lactate
• Vasodilatory shock
• Hypovolemia
• Disseminated intravascular coagulation
• Potential addition of cardiogenic shock
Hypoperfusion and end organ damage including: encephalopathy, acute respiratory distress syndrome (from lung endothelial injury), liver and kidney injury, bowel dysfunction (ileus), bone marrow (thrombocytopenia, leukopenia, dysfunctional neuthrophils, and prolonged clotting times from consumptive coagulopathy)

Fig. 1. Pathophysiology of sepsis and septic shock.
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24.4% of deaths during delivery hospitalization and 38.4% deaths during postpartum readmission.[16]

CAUSES

The causes of sepsis vary by stage of pregnancy and are critical to consider for antibiotic selection and need for source control. By far, according to published data, the most common site of infection associated with sepsis is genitourinary (eg, chorioamnionitis, endometritis, pyelonephritis).[18–21] Other important sources during antepartum include septic abortion, pneumonia (bacterial and viral), and, rarely, central line–associated bloodstream infection. During the delivery hospitalization and postpartum, additional sources include pelvic abscess, pneumonia (bacterial and viral), wound infection (perineal and after cesarean delivery), necrotizing fasciitis, appendicitis, and acute cholecystitis. More rare sources include septic thrombophlebitis, endocarditis, and meningitis.

Bacterial organisms that are most common include *Escherichia coli,* group B streptococcus, and group A streptococcus, followed by unspecified staphylococcus and streptococcus, mixed organisms, and anaerobic organisms.[18,19,22] Sepsis may also be caused by fungi and viruses such as influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

PATIENT EDUCATION

Because most cases of sepsis start outside of the hospital, patient education about warning signs of sepsis is imperative to prompt early medical consultation.[15,16,20] Data from two state maternal mortality committees, Michigan and California, found that many patients who died sought care very late in disease progression or died at home of sepsis.[2,23] The Urgent Maternal Warning Signs are copyrighted by the Alliance for Innovation on Maternal Health, have been translated in more than 80 languages, and are free to use.[24] The Urgent Maternal Warning Signs highlight warning signs for all types of severe maternal morbidity, including sepsis. Data suggest that discharge education is not standardized, and warning signs are not consistently provided.[25,26] In a qualitative study of survivors and support individuals of those who experienced maternal sepsis, every patient experienced one or more of the Urgent Maternal Warning Signs.[27] A major theme identified in that study was that predominant early symptoms may be atypical (eg, severe pain and fatigue). Complicating the presentation for both patient and clinician recognition is that 20–25% of patients do not experience fever (or hypothermia), even among patients who died.[2,13,14] In our opinion, the warning signs most important for patient education are fever and chills, fatigue (inability to perform activities of daily living), severe pain (not managed by pain medication), shortness of breath, and fast heart rate.

Qualitative studies of severe maternal morbidity survivors from the Centers for Disease Control and Prevention's Hear Her campaign found that patient's concerns were commonly dismissed as normal for pregnancy or postpartum and led to significant delays in care.[28] Many symptoms and signs may appear normal for pregnancy or postpartum (eg, elevated white blood cell count, tiredness, postsurgical pain), which can make it difficult for patients with concerning signs to stand out. An initiative to prevent this is the Stop, Look, and Listen Campaign focusing on maternal safety.[29] When a patient presents with concerns, 1) stop assuming that complaints are typical of pregnant or postpartum patients, 2) look and perform a thorough physical examination, and 3) listen to the patient as she tells you what her concerns are in her own words. Using a patient-centered approach may help identify patients presenting with nonspecific concerns that may be signs of developing sepsis.

SCREENING

Most patients who develop sepsis do not have any established risk factors; therefore, screening for abnormal vital signs to identify patients at risk of developing sepsis is a key intervention.[22] Multiple tools are available for screening and are included in Table 1. The ideal tool is one with high sensitivity allowing the identification of most patients with sepsis but with a limited number of false positives to limit unnecessary use of resources. Hospitals should identify a screening system modified for their specific patient population. The use of screening systems for early identification of sepsis has been shown to decrease severe maternal morbidity.[30,31]

Multiple screening tools have been studied to help identify obstetric patients with sepsis. Adult nonpregnancy screening tools adjusted for pregnancy that have been evaluated include SIRS (Systemic Inflammatory Response Syndrome), qSOFA (Quick Sequential Organ Failure Assessment), and MEWS (Modified Early Warning Score). Although SIRS had a range of 92–97% sensitivity to help identify pregnant patients with sepsis, it was limited by a range of 63–79% specificity with a 21–37% false-positive rate.[13,14,32] In pregnancy, qSOFA performed poorly in identifying cases of sepsis with a range of 36–50% sensitivity. Sensitivity

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Table 1. Screening Criteria for Sepsis in Nonpregnant Adults, Pregnancy-Adjusted Sepsis Screening Criteria, and Severe Maternal Morbidity

		Sensitivity/Specificity*			
Screening System	**Criteria**	**Antepartum**	**Delivery Hospitalization**	**Postpartum After Discharge (up to 6 wk)**	**Study Combined Pregnancy and Postpartum Data**
Sepsis screening criteria for nonpregnant adults					
Systemic Inflammatory Response Syndrome (SIRS)[73]	Oral temperature below 36°C (96.8°F) or above 38°C (100.4°F) Heart rate above 90 beats per minute Respiratory rate above 20 breaths/min WBCs above 12,000/mm^3 or below 4,000/mm^3 or above 0% bands Positive if any 2 of 4 criteria are met	77.7%/79% before 20 wk of gestation, 92.2%/76.5% after 20 wk of gestation[14]	93%/63%[32] 96.9%/78.7%[13]	96.9%/78.1% before 3 d postpartum, 87.5%/78.7% after 3 d postpartum[14]	NR
National Early Warning Score (NEWS)[74]	Parameters are given points according to degree of abnormality: Respiratory rate Oxygen saturation Requiring supplemental oxygen Temperature Blood pressure Heart rate AVPU score Scoring system: 0–20 points; low risk (1–4), medium risk (5–6), high risk (7 or above)	NR	NR	NR	33.7%/97.0% to predict ICU admission or death (5 points)[34]
Modified Early Warning Score (MEWS)[75]	Parameters are given points according to degree of abnormality: Systolic blood pressure Heart rate Respiratory rate Temperature AVPU score Score of 5 or more points associated with an increased risk of death, ICU admission, and step-down admission	NR	NR	NR	14.8%/97.0% to predict ICU admission or death (5 points),[34] 100%/50.6% (up to 2 wk postpartum to predict ICU admission)[33]

(*continued*)

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Table 1. Screening Criteria for Sepsis in Nonpregnant Adults, Pregnancy-Adjusted Sepsis Screening Criteria, and Severe Maternal Morbidity (*continued*)

		Sensitivity/Specificity*			
Screening System	**Criteria**	**Antepartum**	**Delivery Hospitalization**	**Postpartum After Discharge (up to 6 wk)**	**Study Combined Pregnancy and Postpartum Data**
Electronic Cardiac Arrest Triage score (eCART)	Parameters are given points according to parameters: age, respiratory rate, heart rate, diastolic blood pressure, systolic blood pressure, number of ICU stays, temperature, pulse pressure index, oxygen saturation, mental status, sodium, potassium, bicarbonate, anion gap, BUN, creatinine, glucose, calcium, WBC count, hemoglobin, platelet count, albumin, total bilirubin, AST, alkaline phosphatase	NR	NR	NR	40.9%/97.0% (score above 0.006 to predict ICU admission or death)[34]
Pregnancy-adjusted sepsis screening tools					
Sepsis-Associated Adverse Outcomes (SAAP) in Pregnancy Screening Tool[37]	Points are given according to when the following are present: WBC count higher than 16.0×10^9/L Systolic blood pressure below 90 mm Hg Respiratory rate 22 breaths/min or higher Heart rate 120 beats per minute or higher Lactic acid 3 mmol/L or higher Abnormal radiography, computed tomography, magnetic resonance imaging, or ultrasound Score of 7 or higher is a positive score and associated with a composite of maternal outcomes	NR	NR	NR	71%/73% to identify severe maternal adverse outcomes[37]
UK Obstetric Surveillance System[19,76]	Temperature below 36°C or above 38°C Heart rate above 100 beats per minutes Respiratory rate above 20 breaths/min	65.1%/89.9% before 20 wk of gestation, 86.1%/89.1% after 20 wk of gestation[14]	92.0%/90.4%[13]	93.8%/94.5% before 3 d postpartum, 74.4%/89.6% after 3 d postpartum[14]	NR

(*continued*)

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Table 1. Screening Criteria for Sepsis in Nonpregnant Adults, Pregnancy-Adjusted Sepsis Screening Criteria, and Severe Maternal Morbidity (*continued*)

		Sensitivity/Specificity*			
Screening System	Criteria	Antepartum	Delivery Hospitalization	Postpartum After Discharge (up to 6 wk)	Study Combined Pregnancy and Postpartum Data
	WBC count above 17×10^9/L or below 4×10^9/L or with 10% immature band forms Positive if any 2 of 4 criteria are met if measures on 2 occasions (at least 4 h apart for temperature, heart rate, respiratory rate)				
California Maternal Quality Care Collaborative[77]	Oral temperature below 36°C (96.8°F) or above 38°C (100.4°F) Heart rate above 110 beats per minutes Respiratory rate above 24 breaths/min WBC above 15,000/mm^3 or below 4,000/mm^3 or above 10% bands Positive if any 2 of 4 criteria are met (sustained for 15 min)	57.8%/93.7% before 20 wk of gestation, 81.6%/92.5% after 20 wk of gestation[14]	90.6%/93.1%[13]	87.5%/96.1% before 3 d postpartum, 68.8%/93.2% after 3 d postpartum[14]	NR
Severe maternal morbidity screening tools					
Maternal Early Warning Trigger Tool (MEWT)[30]	Red criteria (any 1 sustained for more than 20 min) Heart rate less than 50 or more than 130 beats per minutes Respiratory rate less than 10 or more than 30 breaths/min Pulse oximetry below 90% Blood pressure above 160/110 mm Hg Mean arterial pressure below 55 mm Hg Yellow criteria (any 2 sustained for more than 20 min) Heart rate above 110 beats per minutes Respiratory rate above 24/min Pulse oximetry below 93% Blood pressure below 85/45 Temperature below 36°C or above 38°C	45.2%/92.3% before 20 wk of gestation, 75.5%/88.2% after 20 wk of gestation[14]	79.9%/84.2%[13]	68.8%/93.7% before 3 d postpartum, 55.6%/69.1% after 3 d postpartum[14]	31.4%/98.1% to identify ICU admission or death (2 yellow or 1 red criteria)[34]

(*continued*)

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Table 1. Screening Criteria for Sepsis in Nonpregnant Adults, Pregnancy-Adjusted Sepsis Screening Criteria, and Severe Maternal Morbidity (*continued*)

Screening System	Criteria	Sensitivity/Specificity*			
		Antepartum	Delivery Hospitalization	Postpartum After Discharge (up to 6 wk)	Study Combined Pregnancy and Postpartum Data
Safe Motherhood Initiative (modified Maternal Early Warning Criteria)	Systolic blood pressure below 90 or above 160 mm Hg Diastolic blood pressure above 100 mm Hg Heart rate below 50 or above 120 beats per minute Respiratory rate below 10 or more than 24 breaths/min O_2 saturation on room air less than 95% Oliguria less than 35 mL/h×2 h Temperature below 36°C or above 38°C WBC less than 4,000/mm^3 or more than 15,000/mm^3 Maternal agitation, confusion, or unresponsiveness Positive if any 1 criterion is met (sustained for 20 min)	81.9%/69.6% before 20 wk of gestation, 94.4%/63.8% after 20 wk of gestation[14]	82%/87%[32] 96.9%/61.7%[13]	96.9%/62.5% before 3 d postpartum, 90.2%/36.1% after 3 d postpartum[14]	53.3%/88.9% to identify ICU admission or death[34]

WBC, white blood cell; NR, not reported; AVPU, alert, voice, pain, unresponsive; ICU, intensive care unit; BUN, blood urea nitrogen; AST, aspartate transaminase.
* Sensitivity/specificity refers to screening for identification of sepsis unless otherwise specified.

was likely lower because of one criterion included in the qSOFA score, neurologic changes, because neurologic changes are an extremely rare finding in pregnant patients developing sepsis.[32,33] Modified Early Warning Score had variability in performance; one study reported 100% sensitivity and 50.6% specificity, and another study reported 14.8% sensitivity and 97.0% specificity for intensive care unit (ICU) admission.[33,34] Only one study reported the use of NEWS (National Early Warning Score) during pregnancy with a sensitivity and specificity of 33.7% and 97.0%, respectively.[34] The Surviving Sepsis Campaign guidelines recommend against the use of qSOFA compared with SIRS, MEWS, and NEWS.[35]

Other commonly used pregnancy-adjusted criteria to identify sepsis include Maternal Early Warning Criteria, Maternal Early Warning Trigger Tool, California Maternal Quality Care Collaborative criteria, and UK Obstetric Surveillance System. In a recent study of electronic medical record data from 59 diverse hospitals including 1,696 patients with a diagnosis of sepsis during the delivery hospitalization in the United States, most of the tools showed relatively high sensitivity (90.6–96.9%), but their false-positive rate varied widely (6.9–38.3%). The pregnancy-adjusted sepsis screening tools California Maternal Quality Care Collaborative criteria and UK Obstetric Surveillance System had the best balance between sensitivity (90.6% and 92.0%) and false-positive rates (6.9% and 9.6%), respectively, for intrapartum screening. Patients with chorioamnionitis and endometritis were analyzed separately and found to have high rates of sensitivity for most tools (93.6–99.4%), but all had very high rates of false-positives (45.7–92.3%).[13,36] A new screening system, the Sepsis-Associated Adverse Outcomes in Pregnancy Screening Tool, was developed to help identify

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a composite of adverse maternal outcomes (eg, ICU admission, vasopressor use, mechanical ventilation) in patients admitted with infection. The Sepsis-Associated Adverse Outcomes in Pregnancy Screening Tool was found to have a sensitivity and specificity of 71% and 73%, respectively.[37]

When the optimal tool is being selected, it is important to consider the timing of maternal evaluation. In two longitudinal studies of 1,041 pregnant patients and 1,054 postpartum patients, vital signs were taken at specific time periods to analyze expected ranges and trends.[38,39] The heart rate was shown to increase gradually over pregnancy and to abruptly decrease after delivery (within 48–72 hours); this decrease was also demonstrated in a meta-analysis of vital signs throughout pregnancy and postpartum.[40] Consequently, using a single tool throughout pregnancy and postpartum may not be ideal. For example, most pregnancy-adjusted tools have elevated heart rate thresholds (100–120 beats per minute) that may not be appropriate during early pregnancy or the postpartum period. A multisite (71 hospitals) study using electronic medical records to evaluate different scoring systems to identify sepsis in antepartum and postpartum hospitalizations demonstrated that SIRS (not adjusted for pregnancy) had a higher C statistic than pregnancy-adjusted tools at less than 20 weeks of gestation (0.78) and after 3 days postpartum (0.83).[14] During the time when patients are commonly seen in nonobstetric emergency rooms (before 20 weeks of gestation and postpartum), a non–pregnancy-adjusted tool such as the SIRS, NEWS, or MEWS may work best to screen possible cases of sepsis. When there is concern for sepsis, we recommend further assessment with bedside and laboratory evaluation for signs of end-organ injury to confirm diagnosis.

Once sepsis is identified, evaluation for escalation of care is a critical step. In patients who died of sepsis, one of the critical findings has consistently been a delay in escalation of care.[2] Patients were admitted to floor status and later found deceased or in extremis because the early signs of critical illness were not recognized.[2] The Sepsis in Obstetrics score has been prospectively validated to identify patients at risk of ICU admission with a score of 6 points or more.[33,41] A bedside user-friendly version is available at perinatology.com.[42]

DIAGNOSIS

According to Sepsis-3, the diagnosis of sepsis is clinically operationalized by a change in 2 or more points on SOFA as the definition of new-onset organ injury[3]; however, the criteria are not adjusted for pregnancy. The creatinine level to reach 2 points on the SOFA scale is 2.0 mg/dL (meeting criteria for the diagnosis of sepsis), which is likely too high of a threshold for pregnancy, when creatinine levels are normally 0.8 mg/dL or less. Other criteria that may affect the accuracy of SOFA in pregnant patients include thrombocytopenia (less than 150,000 per microliter) and mean arterial pressure (less than 70 mm Hg). Similarly, the Glasgow Coma Scale is not typically assessed and documented in labor and delivery, limiting frequent assessment of neurologic symptoms of end-organ injury. One of the criticisms of the Sepsis-3 definition is that although it is more specific for sepsis and in-hospital mortality, it does not allow early identification and treatment. We recommend prompt treatment with any signs of end-organ injury even if they do not meet SOFA or any other screening criteria.

TREATMENT AND STABILIZATION

After the diagnosis of sepsis, immediate hemodynamic resuscitation is mandatory because even short delays in treatment resulting in hypotension and tissue hypoperfusion increase morbidity and mortality.[35] Simultaneously with resuscitation efforts, obtaining cultures (blood, urine, respiratory, surgical wounds, and others as indicated) and serum lactate and prompt initiation of broad-spectrum antibiotics are recommended.[35] Planning for early source control (eg, delivery in chorioamnionitis, percutaneous drainage of abdominopelvic collections or perirenal abscesses, surgical debridement for necrotizing soft tissue infections, appendectomy, hysterectomy) is of paramount importance and should be addressed in the early stages of treatment after initial stabilization.[43] Figure 2 summarizes the initial management of obstetric patients with sepsis.

Early administration of broad-spectrum antibiotics decreases mortality in patients with sepsis.[44] In a case–control study of seven centers, pregnant patients with sepsis who received antibiotic treatment within 1 hour had an 8% mortality compared with 20% mortality in patients who received antibiotic treatment after 1 hour.[32] Increased mortality with delayed antibiotic administration is consistent with data in the nonpregnant adult population, showing an increase in mortality of 7.6% for each 1-hour delay.[45] Ideally, patients with a high clinical suspicion of sepsis and those with septic shock should receive broad-spectrum antibiotics within 1 hour of presentation.[35,43] For patients who are not in shock and in whom the diagnosis of sepsis is

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unclear, current recommendations for nonpregnant individuals suggest that antibiotics should be started within 3 hours if no alternative diagnosis has been established.[35] Strategies to shorten time to appropriate antimicrobials include having order sets in place for appropriate antibiotic selection, placing antimicrobials into the automated medication-dispensing system, having adequate intravenous access, and using a "code sepsis alert" to indicate to the pharmacy to prioritize, dose, prepare, and deliver antibiotics promptly.[32,46] Box 1 provides antibiotic selection for common infections in pregnant and postpartum patients.

The first resuscitative intervention is fluid administration aiming to achieve a mean arterial blood pressure of 65 mm Hg. Current guidelines recommend 30 mL/kg (predicted or ideal body weight) of crystalloid as the initial fluid strategy, amounting to 1–2 L of crystalloid solutions within the first 3 hours of presentation (Table 2 shows fluid calculations according to ideal body weight).[35,43] Recent evidence suggests that the use of balanced crystalloid solutions (eg, Lactated Ringer or Plasma-Lyte A) decreases the risk of acute kidney injury and need for renal replacement therapy compared with normal saline.[47] The latter is likely secondary to the renal vasoconstrictive effect of saline-induced hyperchloremia. Of note, there is no survival benefit associated with the use of colloids (eg, albumin) in sepsis resuscitation.[48] Further fluid administration beyond the initial 30 mL/kg (1–2 L) should ideally be guided by dynamic measures of preload to identify fluid responsiveness before administration (Box 2).[49]

If hypotension persists despite fluid administration, vasopressor agents should be administered.[35] The Surviving Sepsis Campaign suggests starting vasopressors peripherally to restore mean arterial pressure rather than waiting for central line access.[35] Box 3 gives a protocol for peripheral administration

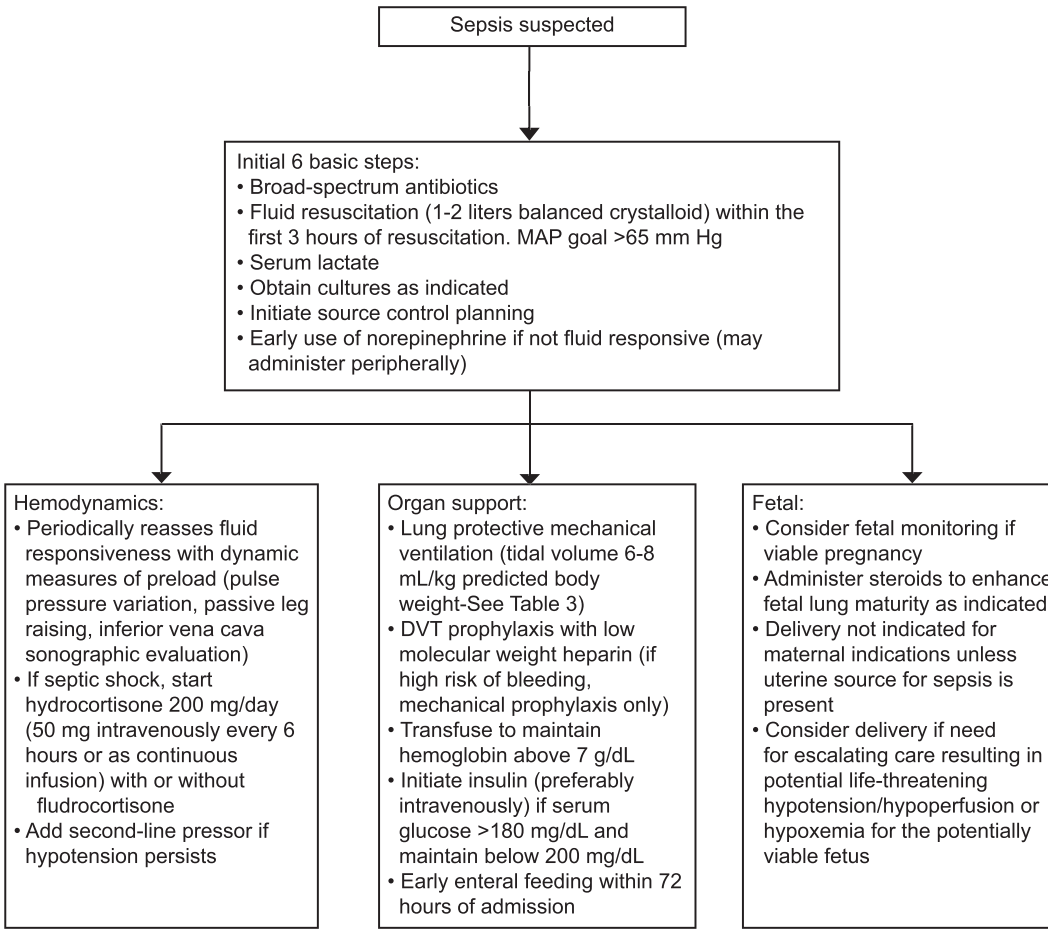
Sepsis suspected
Initial 6 basic steps:
• Broad-spectrum antibiotics
• Fluid resuscitation (1-2 liters balanced crystalloid) within the first 3 hours of resuscitation. MAP goal >65 mm Hg
• Serum lactate
• Obtain cultures as indicated
• Initiate source control planning
• Early use of norepinephrine if not fluid responsive (may administer peripherally)
Hemodynamics:
• Periodically reasses fluid responsiveness with dynamic measures of preload (pulse pressure variation, passive leg raising, inferior vena cava sonographic evaluation)
• If septic shock, start hydrocortisone 200 mg/day (50 mg intravenously every 6 hours or as continuous infusion) with or without fludrocortisone
• Add second-line pressor if hypotension persists
Organ support:
• Lung protective mechanical ventilation (tidal volume 6-8 mL/kg predicted body weight-See Table 3)
• DVT prophylaxis with low molecular weight heparin (if high risk of bleeding, mechanical prophylaxis only)
• Transfuse to maintain hemoglobin above 7 g/dL
• Initiate insulin (preferably intravenously) if serum glucose >180 mg/dL and maintain below 200 mg/dL
• Early enteral feeding within 72 hours of admission
Fetal:
• Consider fetal monitoring if viable pregnancy
• Administer steroids to enhance fetal lung maturity as indicated
• Delivery not indicated for maternal indications unless uterine source for sepsis is present
• Consider delivery if need for escalating care resulting in potential life-threatening hypotension/hypoperfusion or hypoxemia for the potentially viable fetus

Fig. 2. Initial management of pregnant patients with sepsis. MAP, mean arterial blood pressure; DVT, deep vein thrombosis.
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of norepinephrine, which is the first-line vasopressor for management of sepsis in pregnancy.[35,43,50,51] Although norepinephrine improves mean arterial pressure mainly by increasing systemic vascular resistance (α-1 receptor agonism), it also increases cardiac output in 10–20% of patients. Although phenylephrine is commonly used in labor and delivery units, norepinephrine is preferred because phenylephrine use may be associated with higher mortality in sepsis.[52]

As previously discussed, septic shock is clinically defined as having a vasopressor requirement to keep the mean arterial pressure of 65 mm Hg or higher and a lactic acid level above 2 mmol/L despite appropriate fluid resuscitation.[3] Recent guidelines suggest the addition of glucocorticoids for all patients with septic shock regardless of norepinephrine dose.[53] Steroids result in immunomodulation, decreasing the excessive inflammatory response leading to multiorgan failure, and up-regulated catecholamine receptor expression leading to faster shock resolution. Hydrocortisone is the preferred agent at a dose of 200 mg/d (either 50 mg intravenously every 6 hours or as a continuous infusion) for 7 days with or without fludrocortisone 50 micrograms enterally per day.[53] Dose tapering after regimen completion is not required. If glucocorticoid therapy is indicated for induction of fetal lung maturity, betamethasone or dexamethasone should be used according to current obstetric protocols, and hydrocortisone should be held to avoid concurrent administration and exposure to higher doses of glucocorticoids.

Inability to achieve a mean arterial pressure above 65 mm Hg despite fluid therapy, norepinephrine, and steroids commonly will require the addition of second-line vasopressors such as vasopressin or epinephrine.[35] Addition of a second vasopressor will require placement of a central venous catheter if not already done. In nonpregnant individuals, vasopressin is the recommended second-line agent; however, evidence for its use during pregnancy is limited. Despite theoretical concerns of oxytocin receptor activation with vasopressin administration, we believe that in the setting of refractory septic shock during pregnancy, addition of vasopressin as a lifesaving intervention is reasonable. It is important to note that vasopressin is administered as a fixed dose (0.03 units/min) and should not be titrated because higher

Box 1. Commonly Used Empiric Antibiotic and Antiviral Regimens for Pregnant Patients With Sepsis Requiring Hospitalization*†

- Community-acquired meningitis: ceftriaxone and vancomycin
- Community-acquired pneumonia: ceftriaxone and azithromycin
- Endocarditis: vancomycin and gentamicin (add rifampin if prosthetic valve)
- Complicated abdominal–pelvic infections: monotherapy with any of meropenem, imipenem, ertapenem, or piperacillin–tazobactam or combination therapy with levofloxacin plus metronidazole or ceftriaxone plus metronidazole
- Chorioamnionitis: ampicillin plus gentamicin (add metronidazole for anaerobic coverage if cesarean delivery)
- Endometritis: monotherapy with piperacillin–tazobactam, meropenem, ertapenem, or imipenem or combination therapy with ampicillin plus gentamicin plus metronidazole or levofloxacin plus metronidazole
- Urinary tract infection (pyelonephritis): ceftriaxone
- Necrotizing soft tissue infection (eg, necrotizing fasciitis): vancomycin plus meropenem (consider adding clindamycin or linezolid to decrease exotoxin production)
- Influenza pneumonia: oseltamivir
- SARS-CoV-2 pneumonia: remdesivir

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
*When using β-lactams, consider prolonged infusions for maintenance as opposed to conventional bolus therapy.[35]
†Consider avoiding prolonged use of piperacillin–tazobactam with vancomycin because of increased risk of acute kidney injury.[78]

Table 2. Predicted Body Weight and Fluid Administration Based on Height

Height	Predicted Body Weight (kg)*	30 mL/kg (mL)
4′6″	31.7	951
4′7″	34	1,020
4′8″	36.3	1,089
4′9″	38.6	1,158
4′10″	40.9	1,227
4′11″	43.2	1,296
5′0″	45.5	1,365
5′1″	47.8	1,434
5′2″	50.1	1,503
5′3″	52.4	1,572
5′4″	54.7	1,641
5′5″	57	1,710
5′6″	59.3	1,779
5′7″	61.6	1,848
5′8″	63.9	1,917
5′9″	66.2	1,986
5′10″	68.5	2,055
5′11″	70.8	2,124
6′0″	73.1	2,193

* Ideal body weight and predicted body weight are the same for more than 5 ft. Ideal body weight is not applicable for less than 5 ft, so predicted body weight approximations are listed here.

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Box 2. Dynamic Measures of Preload Commonly Used to Predict Fluid Responsiveness

- Pulse pressure variation: applicable only to patients receiving mechanical ventilation, not triggering the ventilator, with an arterial line in place, and with sinus rhythm. Respiratory cycle–induced changes in preload will result in pulse pressure variation exceeding 13% in fluid-responsive patients.[79]
- Passive leg raising: with a noninvasive cardiac output monitor, a passive leg raising maneuver will increase cardiac output–stroke volume by more than 10% only in fluid-responsive patients. May not be reliable during the second half of pregnancy because of uterine compression on the inferior vena cava limiting cardiac filling after passive leg raising.[80]
- Inferior vena cava imaging: respiratory-induced change in inferior vena cava diameter by more than 50% indicates fluid responsiveness.[49]

doses may result in severe vasoconstriction and multiorgan ischemia.[35] Alternatively, epinephrine may be added at a starting dose of 0.02–0.03 micrograms/kg/min titrated to a mean arterial pressure of 65 mm Hg.[35]

Persistent hypoperfusion (cold, clammy extremities; oliguria; worsening hyperlactatemia) despite achieving targeted blood pressure after fluid resuscitation and addition of vasopressors may warrant the use of inotropes to increase cardiac output (eg, low-dose dobutamine at an initial dose of 2.5–5 micrograms/kg/min).[35] Periodic assessment of fluid responsiveness (even if the patient was not fluid responsive previously) with dynamic measurements of preload is key because volume status is dynamic during critical illness. New identification of fluid responsiveness warrants fluid therapy, which may allow vasopressor weaning.

Box 3. Peripheral Administration of Norepinephrine Sample Protocol

- Vein located in forearm. Peripheral line should be at least 18–20 gauge.
- Label infusion as "norepinephrine" and avoid concomitant administration of any other medications or fluids.
- Periodically (every 1–2 h) document blood return through the catheter.
- Maximum dose of norepinephrine of 0.3 micrograms/kg/min (may vary in different centers).
- Maximal duration of infusion 48 h. Longer infusions may require placement of a central venous catheter.
- Evaluate access site every hour for signs of extravasation (skin blanching, acrocyanosis).
- If concern for extravasation: stop infusion, aspirate any residual medication before removing the catheter, and apply subcutaneous phentolamine (α1-antagonist).

Of note, lactic acid level interpretation is challenging in the peripartum period. According to recent data, healthy patients can have significantly elevated lactic acid levels above 4 mmol/L during the second stage of labor and at the time of delivery.[54] The same study suggested that outside of active labor, lactate levels should be expected to be around 2 mmol/L. No studies have evaluated when elevated levels should return to normal. According to high-intensity exercise literature, levels should be expected to return to normal levels within 30 minutes to 1 hour after delivery.[54–57]

FETAL MANAGEMENT AND DELIVERY PLANNING

There is no evidence that in the absence of chorioamnionitis, delivery of the fetus will improve maternal sepsis outcomes. In pregnancies that have reached a gestational age when neonatal resuscitation would be considered, the decision to perform intermittent or continuous fetal monitoring should be discussed with the patient and family members together with a multidisciplinary team including obstetricians, anesthesiologists, and neonatologists. If indicated, betamethasone or dexamethasone may be administered if preterm delivery is anticipated within 7 days.[43] The addition of magnesium sulfate for neuroprotection will depend on sepsis severity and should be individualized because of potential harms, including worsening shock secondary to the vasodilatory effect of magnesium and magnesium toxicity in the setting of sepsis-associated acute kidney injury.

Clinicians must be aware that many nonreassuring fetal heart rate tracings may improve with fluid resuscitation and vasopressor therapy. Although delivery is usually indicated only for obstetric indications (in the absence of chorioamnionitis), delivery may be prudent in unstable patients with sepsis with escalating treatment requirements (eg, significantly increased need of vasopressors, prolonged periods of systemic hypotension, worsening respiratory status resulting in significant hypoxemia). Although delivery is reasonable in the setting of worsening respiratory status resulting in life-threatening hypoxemia, clinicians should not expect an improvement in respiratory function and compliance after delivery.[58] In other words, in the setting of severe respiratory failure secondary

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to sepsis, delivery for maternal indications is not indicated.

POSTSEPSIS SYNDROME AND OTHER SEQUELAE

Postsepsis syndrome is characterized by cognitive dysfunction and physical and psychological impairment. However, many patients may experience some symptoms without the entire constellation of symptoms. The prevalence of postsepsis syndrome or long-term sequelae after sepsis in pregnancy or postpartum is not known. In the nonpregnant adult literature, high rates of physical and cognitive impairment after sepsis hospitalization have been reported among older adults (age 65 years and older).[59,60] Studies including childbearing-aged patients also report disability and psychological sequelae after sepsis. In a Norwegian registry study of people who were working before sepsis hospitalizations linking to sick-leave afterward, at 6 months, 1 year, and 2 years, only 58.6%, 67.5%, and 63.4%, respectively, had returned to work.[61] A Danish population–based study showed that patients were more likely to start a new psychoactive medication after hospitalization if they received mechanical ventilation (12.7%) compared with patients with hospitalization without mechanical ventilation (5.0%) and the general population without hospitalization (0.7%) within the first 3 months after discharge.[62]

Consistent with the adult nonpregnant population, postpartum patients after sepsis have an increased risk of readmission and health care utilization. In a large U.S. database study, postpartum patients who had a sepsis diagnosis during the delivery hospitalization had a 4.5 times odds of readmission (odds ratio [OR] 4.53, 95% CI, 2.48–8.28), 1.9 times odds of emergency department visits (OR 1.85, 95% CI, 1.12–3.04), and 2.3 times odds of postpartum visits (OR 2.27, 95% CI, 1.67–3.08) compared with those without a sepsis diagnosis.[63]

Given the high frequency of mood disorders postpartum[64] and after severe maternal morbidity,[65–67] we recommend that patients receive screening for depression, anxiety, and posttraumatic stress disorder after sepsis for up to 1 year postpartum.

Consistent with Surviving Sepsis Campaign guidelines,[35] we recommend the following:

- Providing patient education about common sequalae after sepsis
- Assessing and referring for physical, cognitive, and psychological sequelae
- Referring to a post–critical illness multidisciplinary clinic if available
- Including in-hospital discharge plans for follow-up with clinicians able to assess, refer, and manage new and long-term sequelae[35]

A common theme in qualitative interviews of maternal sepsis survivors was that many had long-term effects but had difficulty obtaining screening and referrals for treatment.[27] Referrals to physical therapy, occupational therapy, and speech therapy (for difficulty swallowing) and regular assessments of depression, anxiety, and posttraumatic stress disorder are highly recommended. Clinicians should consider providing patients with information about patient advocacy and support organizations such as Sepsis Alliance,[68] End Sepsis: The Legacy of Rory Staunton Foundation,[69] and Begin Again Foundation.[70]

PREVENTION

Prevention of sepsis focuses on prevention of developing infections and prompt treatment when an infection occurs. The Alliance for Innovation on Maternal Health Consensus Bundle on Sepsis in Obstetric Care provides evidence-based interventions to prevent sepsis.[46] Some peripartum indications for antibiotics include preterm premature rupture of membranes, group B streptococcus carrier status, chorioamnionitis, and third- or fourth-degree lacerations.[71] Infection-prevention practices specific for cesarean delivery include the use of electric clippers instead of razor for hair removal, preoperative surgical site skin preparation with an alcohol-based agent, cefazolin administration within 60 minutes before incision for antibiotic prophylaxis, redosing of cefazolin after 1,500-mL estimated blood loss or lengthy procedures (longer than 4 hours), and addition of azithromycin for patients in labor or with ruptured membranes.[46]

Although there are limited data, experts suggest that prompt treatment and a focus on restoration of perfusion and high-quality ICU care may reduce or prevent long-term sequelae of sepsis.[72] Strategies suggested are to focus on early recognition, prompt antibiotic treatment, and restoration of perfusion with fluid resuscitation and vasopressors as needed. Adhering to protocols for active management of pain, agitation, delirium, and early mobilization is also key to reducing short- and long-term sequelae.[72]

CONCLUSION

Sepsis is a leading cause of preventable maternal morbidity and mortality. Three key delays have been associated with maternal deaths: delays in recognition, delays in treatment, and delays in escalation of care.

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Key strategies to early identification include patient education about warning signs requiring immediate medical care and screening for abnormal vital signs that would trigger bedside and laboratory evaluation for end-organ injury. We recommend prompt treatment with any degree of end-organ injury. Once sepsis is identified, critical steps include administering broad-spectrum antibiotic therapy, providing fluid resuscitation, administering norepinephrine to maintain mean arterial pressure above 65 mm Hg, obtaining cultures, monitoring lactic acid levels, and providing early source control. Survivors of sepsis may experience long-term effects, and follow-up for assessment and treatment of postsepsis sequelae is critical.

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